REDACTED VERSION – PUBLICLY FILED

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GLAXO GROUP LIMITED Plaintiff, v. TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES LIMITED Defendants.	)	Civil Action No. 04-171-KAJ **CONFIDENTIAL** **FILED UNDER SEAL**

APPENDIX SUPPORTING TEVA'S BRIEF IN OPPOSITION TO GLAXO'S MOTION FOR SUMMARY JUDGMENT DISMISSING TEVA'S AFFIRMATIVE DEFENSES AND CORRESPONDING COUNTERCLAIM ALLEGING INEQUITABLE CONDUCT DURING THE PROSECUTION OF U.S. PATENT NO. 5,068,249

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Fully Redacted

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PDR®
39
EDITION
1985

PHYSICIANS' DESK REFERENCE®

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EXHIBIT
D

B010

B011

Liquid: Each 5 ml. (1 teaspoonful) contains, in aqueous solution, cimetidine hydrochloride equivalent to cimetidine, 300 mg.; alcohol, 2.8%.
Vials: Each 2 ml. contains, in aqueous solution, cimetidine hydrochloride equivalent to cimetidine, 300 mg.; phenol, 10 mg.
Multiple-dose Vials: 8 ml. (300 mg./2 ml.): Each 2 ml. contains, in aqueous solution, cimetidine hydrochloride equivalent to cimetidine, 300 mg.; phenol, 10 mg.
Single-dose Prefilled Disposable Syringes: Each 2 ml. contains, in aqueous solution, cimetidine hydrochloride equivalent to cimetidine, 300 mg.; phenol, 10 mg.

Clinical Pharmacology: 'Tagamet' (brand of cimetidine) competitively inhibits the action of histamine at the histamine H_2 receptors of the parietal cells and thus represents a new class of pharmacological agents, the histamine H_2-receptor antagonists.
'Tagamet' is not an anticholinergic agent. Studies have shown that 'Tagamet' inhibits both daytime and nocturnal basal gastric acid secretion. 'Tagamet' also inhibits gastric acid secretion stimulated by food, histamine, pentagastrin, caffeine and insulin.

Antisecretory Activity

1) Acid Secretion: *Basal:* Oral 'Tagamet' 300 mg. inhibited basal gastric acid secretion by 100% for at least two hours and by at least 90% throughout the 4 hour study in fasting duodenal ulcer patients.
The gastric pH in all subjects was increased to 5.0 or greater for at least 2¼ hours.
Nocturnal: Nighttime basal secretion in fasting duodenal ulcer patients was inhibited by a 300 mg. dose of 'Tagamet' by 100% for at least one hour and by a mean of 89% over a seven hour period. Gastric pH was increased to 5.0 or greater in most of the patients for three to four hours.
'Tagamet' 300 mg. reduced non-stimulated acid concentration by 70–100% and the non-stimulated volume of gastric secretion by 20–50%.
Food Stimulated: During the first hour after a standard experimental meal, oral 'Tagamet' 300 mg. inhibited gastric acid secretion in duodenal ulcer patients by at least 50%. During the subsequent two hours 'Tagamet' inhibited gastric acid secretion by at least 75%.
The effect of a 300 mg. breakfast dose of 'Tagamet' continued for at least four hours and there was partial suppression of the rise in gastric acid secretion following the luncheon meal in duodenal ulcer patients. This suppression of gastric acid output was enhanced and could be maintained by another 300 mg. dose of 'Tagamet' given with lunch.
In another study, 'Tagamet' 300 mg. given with the meal increased gastric pH as compared with placebo.

	Mean Gastric pH	
	'Tagamet'	Placebo
1 hour	3.5	2.6
2 hours	3.1	1.6
3 hours	3.8	1.9
4 hours	6.1	2.2

The effects of oral 'Tagamet' 300 mg. and propantheline bromide on food-stimulated gastric acid secretion were compared in 7 duodenal ulcer patients. Propantheline bromide was titrated to maximally tolerated dosages—the average dose was 45 mg. 'Tagamet' 300 mg. reduced gastric acid output by 67% vs. 27% ($p < 0.05$) for propantheline bromide.
24-Hour Mean H+ Activity: The 24-hour acid suppression provided by 'Tagamet' with the 400 mg. b.i.d. and 300 mg. q.i.d. regimens is similar (54% and 59%, respectively). However, the 300 mg. q.i.d. regimen produces greater daytime acid suppression, while the 400 mg. b.i.d. regimen results in greater suppression of nocturnal acid secretion. The exact degree and duration of acid suppression needed for healing ulcers are not known.
Chemically Stimulated: Oral 'Tagamet' (brand of cimetidine) significantly inhibited gastric acid secretion stimulated by betazole (an isomer of histamine), pentagastrin, caffeine and insulin as follows:

Stimulant	Stimulant Dose	'Tagamet'	% Inhibition
Betazole	1.5mg/kg (sc)	300mg (po)	85% at 2½ hours
Penta-gastrin	6mcg/kg/hr (iv)	100mg/hr (iv)	60% at 1 hour
Caffeine	5mg/kg/hr (iv)	300mg (po)	100% at 1 hour
Insulin	0.03 units/kg/hr (iv)	100mg/hr (iv)	82% at 1 hour

When food and betazole were used to stimulate secretion, inhibition of hydrogen ion concentration usually ranged from 45–75% and the inhibition of volume ranged from 30–65%.
2) Pepsin: Oral 'Tagamet' 300 mg. reduced total pepsin output as a result of the decrease in volume of gastric juice.
3) Intrinsic Factor: Intrinsic factor secretion was studied with betazole as a stimulant. Oral 'Tagamet' 300 mg. inhibited the rise in intrinsic factor concentration produced by betazole, but some intrinsic factor was secreted at all times.

Other

Lower Esophageal Sphincter Pressure and Gastric Emptying
'Tagamet' has no effect on lower esophageal sphincter (LES) pressure or the rate of gastric emptying.

Pharmacokinetics
'Tagamet' is rapidly absorbed after oral administration and peak levels occur in 45–90 minutes. The half-life of 'Tagamet' is approximately 2 hours. Both oral and parenteral (IV or IM) administration provide comparable periods of therapeutically effective blood levels; blood concentrations remain above that required to provide 80% inhibition of basal gastric acid secretion for 4–5 hours following a dose of 300 mg.
The principal route of excretion of 'Tagamet' is the urine. Following parenteral administration, most of the drug is excreted as the parent compound; following oral administration, the drug is more extensively metabolized, the sulfoxide being the major metabolite. Following a single oral dose, 48% of the drug is recovered from the urine after 24 hours as the parent compound. Following IV or IM administration, approximately 75% of the drug is recovered from the urine after 24 hours as the parent compound.

Clinical Trials:

Duodenal Ulcer
'Tagamet' (brand of cimetidine) has been shown to be effective in the treatment of active duodenal ulcer and, at reduced dosage, in the prevention of recurrent ulcer.
Active Duodenal Ulcer: In worldwide double-blind clinical studies, endoscopically evaluated duodenal ulcer healing rates with 'Tagamet' were consistently higher than those of the placebo controls. In many of the studies, these differences were statistically significant.
Specifically, in various definitive, controlled studies conducted worldwide with daily doses of 'Tagamet' ranging from 800 mg. (400 mg. b.i.d.) to 1200 mg. (300 mg. q.i.d.), healing rates ranged from 36% to 90% at two weeks; 57% to 100% at four weeks; and 58% to 100% at six weeks in duodenal ulcer outpatients. The corresponding healing rates for placebo groups were 8% to 50% at two weeks; 14% to 78% at four weeks; and 23% to 67% at six weeks.
In these studies, 'Tagamet'-treated patients reported a general reduction in both daytime and nocturnal pain, and they also consumed less antacid than did placebo-treated patients. In trials comparing q.i.d. and b.i.d. regimens, there was a nonsignificant trend toward lower antacid use in the q.i.d. group.
While short-term treatment with 'Tagamet' (brand of cimetidine) can result in complete healing of the duodenal ulcer, acute therapy will not prevent ulcer recurrence after 'Tagamet' has been discontinued. Some follow-up studies have reported that the rate of recurrence once therapy was discontinued was slightly higher for patients healed on 'Tagamet' than for patients healed on other forms of therapy; however, the 'Tagamet'-treated patients generally had more severe disease.
Recurrent Duodenal Ulcer: Extended treatment with a reduced dose of 'Tagamet' has been shown to decrease the recurrence of duodenal ulcer.
In double-blind multicenter studies, 400 mg. of 'Tagamet', taken at bedtime, resulted in a significantly lower incidence of duodenal ulcer recurrence in patients treated for up to one year.

PERCENT RECURRING IN EACH QUARTER
Double-Blind Studies Conducted in the U.S.

Quarter	'Tagamet' 400 mg. h.s.	Placebo
I	7% (3/46)	22% (11/49)
II	7% (2/28)	46% (13/28)
III	6% (1/16)	10% (1/10)
IV	– (0/4)	33% (1/3)
Total	13% (6/46)	53% (26/49)

Double-Blind Studies Conducted in Europe

Quarter	'Tagamet' 400 mg. h.s.	Placebo
I	5% (8/179)	32% (108/333)
II	10% (14/143)	24% (45/184)
III	5% (4/78)	21% (17/82)
IV	5% (2/44)	20% (10/49)
Total	16% (28/179)	54% (180/333)

Active Benign Gastric Ulcer
'Tagamet' has been shown to be effective in the short-term treatment of active benign gastric ulcer.
In a multicenter, double-blind U.S. study, patients with endoscopically confirmed benign gastric ulcer were treated with 'Tagamet' 300 mg. four times a day or with placebo for six weeks. Patients were limited to those with ulcers ranging from 0.5–2.5 cm. in size. Endoscopically confirmed healing at six weeks was seen in significantly* more 'Tagamet'-treated patients than in patients receiving placebo, as shown below:

	'Tagamet'	Placebo
week 2	14/63 (22%)	7/63 (11%)
total at week 6	43/65 (66%)*	30/67 (45%)

*$p < 0.05$
Similarly, in worldwide double-blind clinical studies, endoscopically evaluated benign gastric ulcer healing rates were consistently higher with 'Tagamet' than with placebo.
Pathological Hypersecretory Conditions (such as Zollinger-Ellison Syndrome)
'Tagamet' significantly inhibited gastric acid secretion and reduced occurrence of diarrhea, anorexia and pain in patients with pathological hypersecretion associated with Zollinger-Ellison Syndrome, systemic mastocytosis and multiple endocrine adenomas. Use of 'Tagamet' was also followed by healing of intractable ulcers.

Indications:
'Tagamet' (brand of cimetidine) is indicated in:
(1) Short-term treatment of active duodenal ulcer. Since most patients heal within 6-8 weeks, there is rarely reason to use 'Tagamet' at full dosage for longer periods. Concomitant antacids should be given as needed for relief of pain. However, simultaneous administration of 'Tagamet' and antacids is not recommended, since antacids have been reported to interfere with the absorption of 'Tagamet'.
(2) Prophylactic use in duodenal ulcer patients, at reduced dosage, to prevent ulcer recurrence in patients likely to need surgical treatment, e.g., as demonstrated by a history of recurrence or complications, and in patients with concomitant illness in whom surgery would constitute a greater than usual risk. Limitation of use to this population is recommended because the consequences of very long-term use, i.e., beyond one year, of continuous 'Tagamet' therapy are not known.
(3) Short-term treatment of active tric ulcer. There is no informa ing usefulness of treatment longer than 8 weeks.
(4) The treatment of pathologica tory conditions (i.e., Zollinger drome, systemic mastocytos endocrine adenomas).

Contraindications: There are no k indications to the use of 'Tagame cimetidine). However, the physician to the Precautions section regarding t nant, nursing, or pediatric patients.

Precautions: 'Tagamet' (brand o has demonstrated a weak antiandrog animal studies this was manifeste prostate and seminal vesicle weigh there was no impairment of mating or fertility, nor any harm to the fetus mals at doses 9 to 56 times the ful dose of 'Tagamet', as compared with cases of gynecomastia seen in patien one month or longer may be related t In human studies, 'Tagamet' has b have no effect on spermatogenesis, motility, morphology or *in vitro* fert ily.
In a 24-month toxicity study conduct dose levels of 150, 378 and 950 mg. proximately 9 to 56 times the recor man dose), there was a small increas dence of benign Leydig cell tumors group; when the combined drug-tr ind control groups were compared, reached statistical significance. In a 24-month study, there were no di tween the rats receiving 150 mg./kg. ntreated controls. However, a statis ant increase in benign Leydig cel dence was seen in the rats that rece 950 mg./kg./day. These tumors wer control groups as well as treated gr difference became apparent only in Rare instances of cardiac arrhythmi tension have been reported followi dministration of 'Tagamet' HCl (bra dine hydrochloride) Injection by bolus.
Symptomatic response to 'Tagamet' ot preclude the presence of a gastric There have been rare reports of tran of gastric ulcers despite subsequently malignancy.
Reversible confusional states (see A tions) have been observed on occasi ently, but not exclusively, in severel Advancing age (50 or more years) an liver and/or renal disease appear to ing factors. In some patients these tates have been mild and have not ntinuation of 'Tagamet' therapy. It discontinuation was judged necessar tion usually cleared within 3-4 days drawal.
Drug Interactions: 'Tagamet', through an effect on certain microso systems, has been reported to reduc metabolism of warfarin-type an phenytoin, propranolol, chlordiazep pam, lidocaine and theophylline, the elimination and increasing blood le drugs.
Clinically significant effects have b with the warfarin anticoagulants; th monitoring of prothrombin time is r and adjustment of the anticoagulant necessary when 'Tagamet' is admi comitantly. Interaction with phenyt and theophylline has also been rep face adverse clinical effects.
Dosage of the drugs mentioned abo similarly metabolized drugs, particul low therapeutic ratio or in patient and/or hepatic impairment, may re ment when starting or stopping c dministered 'Tagamet' to mainta therapeutic blood levels.

are not known.

(3) **Short-term treatment of active benign gastric ulcer.** There is no information concerning usefulness of treatment periods of longer than 8 weeks.

(4) **The treatment of pathological hypersecretory conditions** (i.e., Zollinger-Ellison Syndrome, systemic mastocytosis, multiple endocrine adenomas).

Contraindications: There are no known contraindications to the use of 'Tagamet' (brand of cimetidine). However, the physician should refer to the Precautions section regarding usage in pregnant, nursing, or pediatric patients.

Precautions: 'Tagamet' (brand of cimetidine) has demonstrated a weak antiandrogenic effect. In animal studies this was manifested as reduced prostate and seminal vesicle weights. However, there was no impairment of mating performance or fertility, nor any harm to the fetus in these animals at doses 9 to 56 times the full therapeutic dose of 'Tagamet', as compared with controls. The cases of gynecomastia seen in patients treated for one month or longer may be related to this effect. In human studies, 'Tagamet' has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or *in vitro* fertilizing capacity.

In a 24-month toxicity study conducted in rats, at dose levels of 150, 378 and 950 mg./kg./day (approximately 9 to 56 times the recommended human dose), there was a small increase in the incidence of benign Leydig cell tumors in each dose group; when the combined drug-treated groups and control groups were compared, this increase reached statistical significance. In a subsequent 24-month study, there were no differences between the rats receiving 150 mg./kg./day and the untreated controls. However, a statistically significant increase in benign Leydig cell tumor incidence was seen in the rats that received 378 and 950 mg./kg./day. These tumors were common in control groups as well as treated groups and the difference became apparent only in aged rats.

Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of 'Tagamet' HCl (brand of cimetidine hydrochloride) Injection by intravenous bolus.

Symptomatic response to 'Tagamet' therapy does not preclude the presence of a gastric malignancy. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy.

Reversible confusional states (see Adverse Reactions) have been observed on occasion, predominantly, but not exclusively, in severely ill patients. Advancing age (50 or more years) and preexisting liver and/or renal disease appear to be contributing factors. In some patients these confusional states have been mild and have not required discontinuation of 'Tagamet' therapy. In cases where discontinuation was judged necessary, the condition usually cleared within 3-4 days of drug withdrawal.

Drug Interactions: 'Tagamet', apparently through an effect on certain microsomal enzyme systems, has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, diazepam, lidocaine and theophylline, thereby delaying elimination and increasing blood levels of these drugs.

Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when 'Tagamet' is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

Dosage of the drugs mentioned above and other similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered 'Tagamet' to maintain optimum therapeutic blood levels.

Additional clinical experience may reveal other drugs affected by the concomitant administration of 'Tagamet'.

Decreased white blood cell counts, including agranulocytosis, have been reported in 'Tagamet'-treated patients who also received antimetabolites, alkylating agents or other drugs and/or treatment known to produce neutropenia.

Usage In Pregnancy: There has been no experience to date with the use of 'Tagamet' in pregnant patients. However, animal studies have demonstrated that 'Tagamet' crosses the placental barrier. Teratology studies (100–950 mg./kg./day) have shown no effects attributable to 'Tagamet' on litter parameters or early development of the young.

'Tagamet' should not be used in pregnant patients or women of childbearing potential unless, in the judgment of the physician, the anticipated benefits outweigh the potential risks.

Nursing Mothers: Cimetidine is secreted in human milk and, as a general rule, nursing should not be undertaken while a patient is on a drug.

Pediatric Use: Clinical experience in children is limited. Therefore, 'Tagamet' therapy cannot be recommended for children under 16, unless, in the judgment of the physician, anticipated benefits outweigh the potential risks. In very limited experience, doses of 20–40 mg./kg. per day have been used.

Adverse Reactions: Mild and transient diarrhea, dizziness, somnolence and rash have been reported in a small number of patients, e.g., approximately 1 in 100, during treatment with 'Tagamet' (brand of cimetidine). A few cases of headache, ranging from mild to severe, have been reported; these cleared on withdrawal of the drug. There have been rare reports of reversible arthralgia and myalgia; exacerbation of joint symptoms in patients with preexisting arthritis has also been reported. Such symptoms have usually been alleviated by a reduction in 'Tagamet' (brand of cimetidine) dosage. A few cases of polymyositis have been reported, but no causal relationship has been established.

Reversible confusional states, e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation, have been reported predominantly, but not exclusively, in severely ill patients. They have usually developed within 2-3 days of initiation of 'Tagamet' therapy and have cleared within 3-4 days of discontinuation of the drug.

Mild gynecomastia has been reported in patients treated for one month or longer. In patients being treated for pathological hypersecretory states, this occurred in about 4 percent of cases while in all others the incidence was 0.3% to 1% in various studies. No evidence of induced endocrine dysfunction was found, and the condition remained unchanged or returned toward normal with continuing 'Tagamet' treatment.

Reversible impotence has been reported in patients with pathological hypersecretory disorders, e.g., Zollinger-Ellison Syndrome, receiving 'Tagamet', particularly in high doses, for at least 12 months (range 12–79 months, mean 38 months). However, in large-scale surveillance studies at regular dosage, the incidence has not exceeded that commonly reported in the general population. Furthermore, in controlled long-term studies in patients receiving a single daily bedtime dose, the incidence of reversible impotence did not differ significantly between the 'Tagamet' and placebo groups.

Reversible alopecia has been reported very rarely.

Decreased white blood cell counts in 'Tagamet'-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge. These patients generally had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 3 per million patients) and a few cases of aplastic anemia have also been reported.

Regularly observed small increases in plasma creatinine and some increases in serum transaminase have been reported. These did not progress with continued therapy and disappeared at the end of therapy.

Rare cases of fever, interstitial nephritis and pancreatitis, which cleared on withdrawal of the drug, have been reported. Adverse hepatic effects have been reported rarely. These were reversible and cholestatic or mixed cholestatic-hepatocellular in nature. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely.

There has been reported a single case of biopsy-proven periportal hepatic fibrosis in a patient receiving 'Tagamet'.

Dosage and Administration:

Duodenal Ulcer

Active Duodenal Ulcer: The recommended adult oral dosage regimen of 'Tagamet' for the routine treatment of duodenal ulcer is 300 mg. four times a day, with meals and at bedtime, the dosage regimen with which U.S. physicians have the most experience. European clinical trials have studied smaller daily dosages: 200 mg. three times a day with meals and 400 mg. at bedtime, as well as 400 mg. twice a day, in the morning and at bedtime. Although the advantages of one regimen over another for a particular patient population have yet to be demonstrated, the 400 mg. twice-a-day regimen may be particularly appropriate for those patients in whom dosing convenience is important.

Concomitant antacids should be given as needed for relief of pain. However, simultaneous administration of 'Tagamet' and antacids is not recommended, since antacids have been reported to interfere with the absorption of 'Tagamet' (brand of cimetidine).

While healing with 'Tagamet' often occurs during the first week or two, treatment should be continued for 4–6 weeks unless healing has been demonstrated by endoscopic examination.

Prophylaxis of Recurrent Duodenal Ulcer: In those patients in whom prophylactic use is indicated, one 400 mg. tablet or two 200 mg. tablets at bedtime is recommended. Prophylactic treatment with higher or more frequent doses does not improve effectiveness.

Active Benign Gastric Ulcer

The recommended adult oral dosage for short-term treatment of active benign gastric ulcer is 300 mg. four times a day with meals and at bedtime. Controlled clinical studies were limited to six weeks of treatment (see Clinical Trials). Symptomatic response to 'Tagamet' does not preclude the presence of a gastric malignancy. It is important to follow gastric ulcer patients to assure rapid progress to complete healing.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison Syndrome)

Recommended adult oral dosage: 300 mg. four times a day with meals and at bedtime. In some patients it may be necessary to administer 'Tagamet' 300 mg. doses more frequently. Doses should be adjusted to individual patient needs, but should not usually exceed 2400 mg. per day and should continue as long as clinically indicated.

Parenteral Administration

In some hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or in patients who are unable to take oral medication, 'Tagamet' may be administered parenterally according to the following recommendations:

Intramuscular Injection: 300 mg. q 6 hours (no dilution necessary). Transient pain at the site of injection has been reported.

Intermittent Intravenous Infusion: 300 mg. q 6 hours. Dilute 'Tagamet' HCl Injection, 300 mg., in 100 ml. of Dextrose Injection (5%) or other compatible i.v. solution (see Stability of 'Tagamet' HCl Injection) and infuse over 15–20 minutes. In some patients it may be necessary to increase dosage. When this is necessary the increases should be made by more frequent administration of a 300 mg. dose, but should not

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EXHIBIT E

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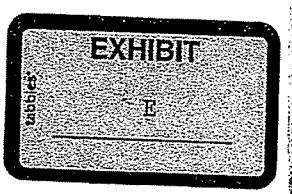

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B013

of all of the following adverse reactions have been observed
ch every phenothiazine derivative, but they have been
orted with one or more and should be borne in mind when
gs of this class are administered: extrapyramidal symp-
ms (opisthotonos, oculogyric crisis, hyperreflexia, dysto-
a, akathisia, dyskinesia, parkinsonism) some of which
re lasted months and even years—particularly in elderly
tients with previous brain damage; grand mal and petit
al convulsions, particularly in patients with EEG abnor-
alities or history of such disorders; altered cerebrospinal
id proteins; cerebral edema; intensification and prolonga-
n of the action of central nervous system depressants (opi-
es, analgesics, antihistamines, barbiturates, alcohol), atro-
ine, heat, organophosphorus insecticides; autonomic reac-
ns (dryness of mouth, nasal congestion, headache, nausea,
nstipation, obstipation, adynamic ileus, ejaculatory disor-
der/impotence, priapism, atonic colon, urinary retention,
osis and mydriasis); reactivation of psychotic processes,
atonic-like states; hypotension (sometimes fatal); cardiac
rest; blood dyscrasias (pancytopenia, thrombocytopenic
rpura, leukopenia, agranulocytosis, eosinophilia, hemo-
ic anemia, aplastic anemia); liver damage (jaundice, bili-
y dasis); endocrine disturbances (hyperglycemia, hypogly-
emia, glycosuria, lactation, galactorrhea, gynecomastia,
enstrual irregularities, false positive pregnancy tests); skin
isorders (photosensitivity, itching, erythema, urticaria,
zema up to exfoliative dermatitis); other allergic reactions
sthma, laryngeal edema, angioneurotic edema, anaphylac-
id reactions); peripheral edema; reversed epinephrine ef-
ct; hyperpyrexia; mild fever after large I.M. doses; in-
reased appetite; increased weight; a systemic lupus ery-
hematosus-like syndrome; pigmentary retinopathy; with
rolonged administration of substantial doses, skin pigmen-
ation, epithelial keratopathy, and lenticular and corneal
eposits.

KG changes—particularly nonspecific, usually reversible
Q and T wave distortions—have been observed in some pa-
ents receiving phenothiazine tranquilizers. Although phe-
thiazines cause neither psychic nor physical dependence,
oken discontinuance in long-term psychiatric patients
ay cause temporary symptoms, e.g., nausea and vomiting,
ainness, tremulousness.

re occurrences of neuroleptic malignant syndrome (NMS)
ve been reported in patients receiving neuroleptic drugs.
is syndrome is comprised of the symptom complex of hy-
rthermia, altered consciousness, muscular rigidity and
utonomic dysfunction and is potentially fatal.

ote: There have been occasional reports of sudden death
patients receiving phenothiazines. In some cases, the
ath appeared to be cardiac arrest or asphyxia due to fail-
re of the cough reflex.

DOSAGE AND ADMINISTRATION—ADULTS

Dosage should be adjusted to the needs of the individual. The
west effective dosage should always be used. Dosage should
be increased more gradually in debilitated or emaciated pa-
tients. When maximum response is achieved, dosage may be
reduced gradually to a maintenance level. Because of the
inherent long action of the drug, patients may be controlled
on convenient b.i.d. administration; some patients may be
maintained on once-a-day administration.

When Stelazine (trifluoperazine HCl, SK&F) is administered
by intramuscular injection, equivalent oral dosage may be
substituted once symptoms have been controlled.

Note: Although there is little likelihood of contact dermati-
tis due to the drug, persons with known sensitivity to pheno-
thiazine drugs should avoid direct contact.

Elderly Patients: In general, dosages in the lower range are
sufficient for most elderly patients. Since they appear to be
more susceptible to hypotension and neuromuscular reac-
tions, such patients should be observed closely. Dosage
should be tailored to the individual, response carefully moni-
tored, and dosage adjusted accordingly. Dosage should be
increased more gradually in elderly patients.

Non-psychotic Anxiety

Usual dosage is 1 or 2 mg. twice daily. Do not administer at
doses of more than 6 mg. per day or for longer than 12 weeks.

Psychotic Disorders

Oral: Usual starting dosage is 2 mg. to 5 mg. b.i.d. (Small or
emaciated patients should always be started on the lower
dosage.)

Most patients will show optimum response on 15 mg. or 20
mg. daily, although a few may require 40 mg. a day or more.
Optimum therapeutic dosage levels should be reached
within two or three weeks.

When the Concentrate dosage form is to be used, it should be
added to 60 ml. (2 fl. oz.) or more of diluent *just prior to ad-
ministration* to insure palatability and stability. Vehicles
suggested for dilution are: tomato or fruit juice, milk, simple
syrup, orange syrup, carbonated beverages, coffee, tea, or
water. Semisolid foods (soup, puddings, etc.) may also be
used.

Intramuscular (for prompt control of severe symptoms):
Usual dosage is 1 mg. to 2 mg. (½-1 ml.) by deep intramuscu-
lar injection q4-6h, p.r.n. More than 6 mg. within 24 hours is
rarely necessary.

Only in very exceptional cases should intramuscular dosage
exceed 10 mg. within 24 hours. Injections should not be given
at intervals of less than 4 hours because of a possible cumula-
tive effect.

Note: Stelazine (trifluoperazine HCl, SK&F) Injection has
been usually well tolerated and there is little, if any, pain
and irritation at the site of injection.

The Injection should be protected from light. Exposure may
cause discoloration. Slight yellowish discoloration will not
alter potency or efficacy. If markedly discolored, the solution
should be discarded.

DOSAGE AND ADMINISTRATION—PSYCHOTIC CHILDREN

Dosage should be adjusted to the weight of the child and se-
verity of the symptoms. These dosages are for children, ages
6 to 12, who are hospitalized or under close supervision.

Oral: The starting dosage is 1 mg. administered once a day
or b.i.d. Dosage may be increased gradually until symptoms
are controlled or until side effects become troublesome.

While it is usually not necessary to exceed dosages of 15 mg.
daily, some older children with severe symptoms may re-
quire higher dosages.

Intramuscular: There has been little experience with the
use of Stelazine (trifluoperazine HCl, SK&F) Injection in
children. However, if it is necessary to achieve rapid control
of severe symptoms, 1 mg. (½ ml.) of the drug may be admin-
istered intramuscularly once or twice a day.

OVERDOSAGE

(See also under Adverse Reactions.)

Symptoms—Primarily involvement of the extrapyramidal
mechanism producing some of the dystonic reactions de-
scribed above. Symptoms of central nervous system depres-
sion to the point of somnolence or coma. Agitation and rest-
lessness may also occur. Other possible manifestations in-
clude convulsions, EKG changes and cardiac arrhythmias,
fever, and autonomic reactions such as hypotension, dry
mouth and ileus.

Treatment—It is important to determine other medications
taken by the patient since multiple dose therapy is common
in overdosage situations. Treatment is essentially symptom-
atic and supportive. Early gastric lavage is helpful. Keep
patient under observation and maintain an open airway,
since involvement of the extrapyramidal mechanism may
produce dysphagia and respiratory difficulty in severe over-
dosage. **Do not attempt to induce emesis because a dystonic
reaction of the head or neck may develop that could result in
aspiration of vomitus.** Extrapyramidal symptoms may be
treated with anti-parkinsonism drugs, barbiturates, or Bena-
dryl‖. See prescribing information for these products. Care
should be taken to avoid increasing respiratory depression. If
administration of a stimulant is desirable, amphetamine,
dextroamphetamine, or caffeine with sodium benzoate is
recommended. Stimulants that may cause convulsions (e.g.,
picrotoxin or pentylenetetrazol) should be avoided.

If hypotension occurs, the standard measures for managing
circulatory shock should be initiated. If it is desirable to ad-
minister a vasoconstrictor, Levophed* and Neo-Synephrine†
are most suitable. Other pressor agents, including epineph-
rine, are not recommended because phenothiazine deriva-
tives may reverse the usual elevating action of these agents
and cause a further lowering of blood pressure.

Limited experience indicates that phenothiazines are *not*
dialyzable.

HOW SUPPLIED

Tablets, 1 mg. and 2 mg., in bottles of 100 and 1000; in Single
Unit Packages of 100 (intended for institutional use only).
For psychiatric patients who are hospitalized or under close
supervision:

Tablets, 5 mg. and 10 mg., in bottles of 100 and 1000; in Sin-
gle Unit Packages of 100 (intended for institutional use only).
Multiple-dose Vials, 10 ml. (2 mg./ml.), in boxes of 1 and 20.
Concentrate, 10 mg./ml., in 2 fl. oz. bottles and in cartons of
12 bottles.

Each bottle is packaged with a graduated dropper.

The Concentrate form is light-sensitive. For this reason, it
should be protected from light and dispensed in amber bot-
tles. *Refrigeration is not required.*

* Norepinephrine bitartrate, Winthrop-Breon Laboratories.
† Phenylephrine hydrochloride, Winthrop-Breon Laborato-
ries.
‡ Phenytoin, Parke-Davis.
§ Metrizamide, Winthrop-Breon Laboratories.
‖ Diphenhydramine hydrochloride, Parke-Davis.

SZ:L60

Shown in Product Identification Section, page 431

TAGAMET® ℞

[tag'ah-met]

(brand of cimetidine tablets
cimetidine hydrochloride liquid and
cimetidine hydrochloride injection)

PRODUCT OVERVIEW

KEY FACTS

'Tagamet' is a histamine H_2 receptor antagonist which inhib-
its both daytime and nocturnal basal gastric acid secretion.
'Tagament' also inhibits gastric acid secretion stimulated by
food, histamine, pentagastrin, caffeine and insulin.

MAJOR USES

'Tagamet' is indicated in the short-term treatment of active
duodenal ulcer, and promotes healing in most patients
within 4 weeks. The 800 mg. h.s. dosing regimen is the regi-
men of choice for most patients as it provides a high healing
rate, maximal pain relief, a decreased potential for drug in-
teractions and maximal patient convenience. After healing
of active ulcer, patients have been maintained on continued
treatment with 'Tagamet' 400 mg. at bedtime for periods of
up to five years. 'Tagamet' 300 mg. q.i.d. has proven effective
in the treatment of active benign gastric ulcer and pathologi-
cal hypersecretory conditions (i.e., Zollinger-Ellison Syn-
drome).

In hospitalized patients with pathological hypersecretory
conditions or intractable ulcers, or in patients who are un-
able to take oral medication, 'Tagamet' may be administered
parenterally.

SAFETY INFORMATION

There are no known contraindications to the use of 'Taga-
met'.

PRESCRIBING INFORMATION

TAGAMET® ℞

[tag'ah-met]

(brand of cimetidine tablets
cimetidine hydrochloride liquid and
cimetidine hydrochloride injection)

('Tagamet' is a product of SK&F Lab Co., Cidra, P.R. 00639,
Subsidiary of SmithKline Beckman Corporation,
Philadelphia, Pa.)

DESCRIPTION

'Tagamet' (brand of cimetidine) is a histamine H_2 receptor
antagonist. Chemically it is N''-cyano-N-methyl-N'-[2-[[(5-
methyl-1H-imidazol-4-yl) methyl] thio]-ethyl]-guanidine.
The empirical formula for cimetidine is $C_{10}H_{16}N_6S$ and for
cimetidine hydrochloride, $C_{10}H_{16}N_6SHCl$; these represent
molecular weights of 252.34 and 288.80, respectively.
Cimetidine contains an imidazole ring, and is chemically
related to histamine.

(The liquid and injection dosage forms contain cimetidine as
the hydrochloride.)

Cimetidine has a bitter taste and characteristic odor.

Tablets: Each light green, film-coated tablet contains
cimetidine as follows: 200 mg.—round, imprinted with the
product name TAGAMET, SKF and 200; 300 mg.—round,
imprinted with the product name TAGAMET, SKF and 300;
400 mg.—capsule-shaped, imprinted with the product name
TAGAMET, SKF and 400; 800 mg.—oval Tiltab® tablets,
imprinted with the product name TAGAMET, SKF and 800.
Inactive ingredients consist of cellulose, D&C Yellow No. 10,
FD&C Blue No. 2, FD&C Yellow No. 6, hydroxypropyl meth-
ylcellulose, iron oxides, magnesium stearate, povidone, pro-
pylene glycol, sodium lauryl sulfate, sodium starch glycolate,
starch, titanium dioxide and trace amounts of other inactive
ingredients.

Liquid: Each 5 ml. (one teaspoonful) of clear, light orange,
mint-peach flavored liquid contains cimetidine hydrochlo-
ride equivalent to cimetidine, 300 mg.; alcohol, 2.8%. Inac-
tive ingredients consist of FD&C Yellow No. 6, flavors, meth-
ylparaben, polyoxyethylene polyoxypropylene glycol,
propylene glycol, propylparaben, saccharin sodium, sodium
chloride, sodium phosphate, sorbitol and water.

Vials: Each 2 ml. contains, in aqueous solution, cimetidine
hydrochloride equivalent to cimetidine, 300 mg.; phenol, 10
mg.

Multiple-dose Vials: 8 ml. (300 mg./2 ml.): Each 2 ml. con-
tains, in aqueous solution, cimetidine hydrochloride equiva-
lent to cimetidine, 300 mg.; phenol, 10 mg.

Single-dose Prefilled Disposable Syringes: Each 2 ml. con-
tains, in aqueous solution, cimetidine hydrochloride equiva-
lent to cimetidine, 300 mg.; phenol, 10 mg.

Single-dose Premixed Plastic Containers: Each 50 ml. con-
tains cimetidine hydrochloride equivalent to 300 mg. cimeti-
dine and 0.45 grams sodium chloride.

No preservative has been added.

The plastic container is fabricated from specially formulated
polyvinyl chloride. The amount of water that can permeate
from inside the container into the overwrap is insufficient to

Continued on next page

Smith Kline & French—Cont.

affect the solution significantly. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, e.g., di 2-ethylhexyl phthalate (DEHP), up to 5 parts per million. However, the safety of the plastic has been confirmed in tests in animals according to the USP biological tests for plastic containers as well as by tissue culture toxicity studies.

ADD-Vantage® * Vials: Each 2 ml. contains, in aqueous solution, cimetidine hydrochloride equivalent to cimetidine, 300 mg.; phenol, 10 mg.

* ADD-Vantage® is a trademark of Abbott Laboratories.

CLINICAL PHARMACOLOGY

'Tagamet' (brand of cimetidine) competitively inhibits the action of histamine at the histamine H_2 receptors of the parietal cells and thus is a histamine H_2-receptor antagonist. 'Tagamet' is not an anticholinergic agent. Studies have shown that 'Tagamet' inhibits both daytime and nocturnal basal gastric acid secretion. 'Tagamet' also inhibits gastric acid secretion stimulated by food, histamine, pentagastrin, caffeine and insulin.

Antisecretory Activity

1) **Acid Secretion:** *Nocturnal:* 'Tagamet' 800 mg. at bedtime reduces mean hourly H^+ activity by greater than 85% over an eight-hour period in duodenal ulcer patients, with no effect on daytime acid secretion. 'Tagamet' 1600 mg. h.s. produces 100% inhibition of mean hourly H^+ activity over an eight-hour period in duodenal ulcer patients, but also reduces H^+ activity by 35% for an additional five hours into the following morning. 'Tagamet' 400 mg. b.i.d. and 300 mg. q.i.d. decrease nocturnal acid secretion in a dose-related manner, i.e., 47%–83% over a six- to eight-hour period and 54% over a nine-hour period, respectively.

Food Stimulated: During the first hour after a standard experimental meal, oral 'Tagamet' 300 mg. inhibited gastric acid secretion in duodenal ulcer patients by at least 50%. During the subsequent two hours 'Tagamet' inhibited gastric acid secretion by at least 75%.

The effect of a 300 mg. breakfast dose of 'Tagamet' continued for at least four hours and there was partial suppression of the rise in gastric acid secretion following the luncheon meal in duodenal ulcer patients. This suppression of gastric acid output was enhanced and could be maintained by another 300 mg. dose of 'Tagamet' given with lunch.

In another study, 'Tagamet' 300 mg. given with the meal increased gastric pH as compared with placebo.

	Mean Gastric pH	
	'Tagamet'	Placebo
1 hour	3.5	2.6
2 hours	3.1	1.6
3 hours	3.8	1.9
4 hours	6.1	2.2

24-Hour Mean H^+ Activity: 'Tagamet' 800 mg. h.s., 400 mg. b.i.d. and 300 mg. q.i.d. all provide a similar, moderate (less than 60%) level of 24-hour acid suppression. However, the 800 mg. h.s. regimen exerts its entire effect on nocturnal acid, and does not affect daytime gastric physiology.

Chemically Stimulated: Oral 'Tagamet' (brand of cimetidine) significantly inhibited gastric acid secretion stimulated by betazole (an isomer of histamine), pentagastrin, caffeine and insulin as follows:

Stimulant	Stimulant Dose	'Tagamet'	% Inhibition
Betazole	1.5mg/kg (sc)	300mg (po)	85% at 2½ hours
Penta-gastrin	6mcg/kg/hr (iv)	100mg/hr (iv)	60% at 1 hour
Caffeine	5mg/kg/hr (iv)	300mg (po)	100% at 1 hour
Insulin	0.03 units/kg/hr (iv)	100mg/hr (iv)	82% at 1 hour

When food and betazole were used to stimulate secretion, inhibition of hydrogen ion concentration usually ranged from 45–75% and the inhibition of volume ranged from 30–65%.

2) **Pepsin:** Oral 'Tagamet' 300 mg. reduced total pepsin output as a result of the decrease in volume of gastric juice.

3) **Intrinsic Factor:** Intrinsic factor secretion was studied with betazole as a stimulant. Oral 'Tagamet' 300 mg. inhibited the rise in intrinsic factor concentration produced by betazole, but some intrinsic factor was secreted at all times.

Other

Lower Esophageal Sphincter Pressure and Gastric Emptying

'Tagamet' has no effect on lower esophageal sphincter (LES) pressure or the rate of gastric emptying.

Pharmacokinetics

'Tagamet' is rapidly absorbed after oral administration and peak levels occur in 45–90 minutes. The half-life of 'Tagamet' is approximately 2 hours. Both oral and parenteral (IV or IM) administration provide comparable periods of therapeutically effective blood levels; blood concentrations remain above that required to provide 80% inhibition of basal gastric acid secretion for 4–5 hours following a dose of 300 mg.

The principal route of excretion of 'Tagamet' is the urine. Following parenteral administration, most of the drug is excreted as the parent compound; following oral administration, the drug is more extensively metabolized, the sulfoxide being the major metabolite. Following a single oral dose, 48% of the drug is recovered from the urine after 24 hours as the parent compound. Following IV or IM administration, approximately 75% of the drug is recovered from the urine after 24 hours as the parent compound.

CLINICAL TRIALS

Duodenal Ulcer

'Tagamet' (brand of cimetidine) has been shown to be effective in the treatment of active duodenal ulcer and, at reduced dosage, in maintenance therapy following healing of active ulcers.

Active Duodenal Ulcer: 'Tagamet' accelerates the rate of duodenal ulcer healing. Healing rates reported in U.S. and foreign controlled trials with 'Tagamet' are summarized below, beginning with the regimen providing the lowest nocturnal dose.

Duodenal Ulcer Healing Rates
with Various 'Tagamet' Dosage Regimens*

Regimen	300 mg. q.i.d.	400 mg. b.i.d.	800 mg. h.s.	1600 mg. h.s.
week 4	68%	73%	80%	86%
week 6	80%	80%	89%	—
week 8	—	92%	94%	—

* Averages from controlled clinical trials.

A U.S., double-blind, placebo-controlled, dose-ranging study demonstrated that all once-daily at bedtime (h.s.) 'Tagamet' regimens were superior to placebo in ulcer healing and that 'Tagamet' 800 mg. h.s. healed 75% of patients at four weeks. The healing rate with 800 mg. h.s. was significantly superior to 400 mg. h.s. (66%) and not significantly different from 1600 mg. h.s. (81%).

In the U.S. dose-ranging trial, over 80% of patients receiving 'Tagamet' 800 mg. h.s. experienced nocturnal pain relief after one day. Relief from daytime pain was reported in approximately 70% of patients after two days. As with ulcer healing, the 800 mg. h.s. dose was superior to 400 mg. h.s. and not different from 1600 mg. h.s.

In foreign, double-blind studies with 'Tagamet' 800 mg. h.s., 79–85% of patients were healed at four weeks.

While short-term treatment with 'Tagamet' (brand of cimetidine) can result in complete healing of the duodenal ulcer, acute therapy will not prevent ulcer recurrence after 'Tagamet' has been discontinued. Some follow-up studies have reported that the rate of recurrence once therapy was discontinued was slightly higher for patients healed on 'Tagamet' than for patients healed on other forms of therapy; however, the 'Tagamet'-treated patients generally had more severe disease.

Maintenance Therapy in Duodenal Ulcer: Treatment with a reduced dose of 'Tagamet' has been proven effective as maintenance therapy following healing of active duodenal ulcers.

In numerous placebo-controlled studies conducted worldwide, the percent of patients with observed ulcers at the end of one year's therapy with 'Tagamet' 400 mg. h.s. was significantly lower (10%–45%) than in patients receiving placebo (44%–70%). Thus, from 55% to 90% of patients were maintained free of observed ulcers at the end of one year with 'Tagamet' 400 mg. h.s.

Factors such as smoking, duration and severity of disease, gender, and genetic traits may contribute to variations in actual percentages.

Trials of other anti-ulcer therapy, whether placebo-controlled, positive-controlled or open, have demonstrated a range of results similar to that seen with 'Tagamet'.

Active Benign Gastric Ulcer

'Tagamet' has been shown to be effective in the short-term treatment of active benign gastric ulcer.

In a multicenter, double-blind U.S. study, patients with endoscopically confirmed benign gastric ulcer were treated with 'Tagamet' 300 mg. four times a day or with placebo for six weeks. Patients were limited to those with ulcers ranging from 0.5–2.5 cm. in size. Endoscopically confirmed healing at six weeks was seen in significantly* more 'Tagamet'-treated patients than in patients receiving placebo, as shown below:

	'Tagamet'	Placebo
week 2	14/63 (22%)	7/63 (11%)
total at week 6	43/65 (66%)*	30/67 (45%)

*$p < 0.05$

Similarly, in worldwide double-blind clinical studies, endoscopically evaluated benign gastric ulcer healing rates were consistently higher with 'Tagamet' than with placebo.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison Syndrome)

'Tagamet' significantly inhibited gastric acid secretion and reduced occurrence of diarrhea, anorexia and pain in patients with pathological hypersecretion associated with Zollinger-Ellison Syndrome, systemic mastocytosis and multiple endocrine adenomas. Use of 'Tagamet' was also followed by healing of intractable ulcers.

INDICATIONS

'Tagamet' (brand of cimetidine) is indicated in:

(1) **Short-term treatment of active duodenal ulcer.** Most patients heal within 4 weeks and there is rarely reason to use 'Tagamet' at full dosage for longer than 6–8 weeks (see Dosage and Administration—Duodenal Ulcer). Concomitant antacids should be given as needed for relief of pain. However, simultaneous administration of 'Tagamet' and antacids is not recommended, since antacids have been reported to interfere with the absorption of 'Tagamet'.

(2) **Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of active ulcer.** Patients have been maintained on continued treatment with 'Tagamet' 400 mg. h.s. for periods of up to five years.

(3) **Short-term treatment of active benign gastric ulcer.** There is no information concerning usefulness of treatment periods of longer than 8 weeks.

(4) **The treatment of pathological hypersecretory conditions** (i.e., Zollinger-Ellison Syndrome, systemic mastocytosis, multiple endocrine adenomas).

CONTRAINDICATIONS

There are no known contraindications to the use of 'Tagamet' (brand of cimetidine). However, the physician should refer to the Precautions section regarding usage in pregnant, nursing, or pediatric patients.

PRECAUTIONS

'Tagamet' (brand of cimetidine) has demonstrated a weak antiandrogenic effect. In animal studies this was manifested as reduced prostate and seminal vesicle weights. However, there was no impairment of mating performance or fertility, nor any harm to the fetus in these animals at doses 9 to 56 times the full therapeutic dose of 'Tagamet', as compared with controls. The cases of gynecomastia seen in patients treated for one month or longer may be related to this effect.

In human studies, 'Tagamet' has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or *in vitro* fertilizing capacity.

In a 24-month toxicity study conducted in rats, at dose levels of 150, 378 and 950 mg./kg./day (approximately 9 to 56 times the recommended human dose), there was a small increase in the incidence of benign Leydig cell tumors in each dose group; when the combined drug-treated groups and control groups were compared, this increase reached statistical significance. In a subsequent 24-month study, there were no differences between the rats receiving 150 mg./kg./day and the untreated controls. However, a statistically significant increase in benign Leydig cell tumor incidence was seen in the rats that received 378 and 950 mg./kg./day. These tumors were common in control groups as well as treated groups and the difference became apparent only in aged rats.

Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of 'Tagamet' HCl (brand of cimetidine hydrochloride) Injection by intravenous bolus.

Symptomatic response to 'Tagamet' therapy does not preclude the presence of a gastric malignancy. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy.

Reversible confusional states (see Adverse Reactions) have been observed on occasion, predominantly, but not exclusively, in severely ill patients. Advancing age (50 or more years) and preexisting liver and/or renal disease appear to be contributing factors. In some patients these confusional states have been mild and have not required discontinuation of 'Tagamet' therapy. In cases where discontinuation was judged necessary, the condition usually cleared within 3-4 days of drug withdrawal.

Drug Interactions: 'Tagamet', apparently through an effect on certain microsomal enzyme systems, has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, diazepam, lidocaine, theophylline and metronidazole, thereby delaying elimination and increasing blood levels of these drugs. Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when 'Tagamet' is adminis-

CERTIFICATE OF SERVICE

I, Karen E. Keller, Esquire, hereby certify that on August 4, 2006, I caused to be electronically filed a true and correct copy of the foregoing document with the Clerk of the Court using CM/ECF, which will send notification that such filing is available for viewing and downloading to the following counsel of record:

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I further certify that on June 30, 2006, I caused a copy of the foregoing document to be served by hand delivery on the above-listed counsel of record and on the following non-registered participants in the manner indicated:

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